### Reality check of high-risk strategies for primary prevention of cardiovascular disease in Europe and United States

<table>
<thead>
<tr>
<th>Journal:</th>
<th>BMJ Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manuscript ID:</td>
<td>bmjopen-2014-005991</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Research</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>27-Jun-2014</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Mortensen, Martin; Aarhus University Hospital, Cardiology Falk, Erling; Aarhus University Hospital, Cardiology</td>
</tr>
<tr>
<td>Primary Subject Heading:</td>
<td>Cardiovascular medicine</td>
</tr>
<tr>
<td>Secondary Subject Heading:</td>
<td>General practice / Family practice, Public health</td>
</tr>
<tr>
<td>Keywords:</td>
<td>PREVENTIVE MEDICINE, Coronary heart disease &lt; CARDIOLOGY, Ischaemic heart disease &lt; CARDIOLOGY, Myocardial infarction &lt; CARDIOLOGY, VASCULAR MEDICINE</td>
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Reality check of high-risk strategies for primary prevention of cardiovascular disease in Europe and United States

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ABSTRACT

Objective
To determine the detection rate (sensitivity) of the high-risk strategy recommended in the European (ESC and NICE/UK) and American (ACC/AHA) guidelines on cardiovascular disease (CVD) prevention. In particular, to evaluate the ability to ensure statin therapy to contemporary Europeans destined for a first cardiovascular event.

Design
393 consecutive statin-naïve, non-diabetic, CVD-free patients hospitalized for a first myocardial infarction (MI). We assumed they had undergone a health check the day before their MI and estimated the predicted risk.

Primary outcome
Sensitivity of the risk-based eligibility for primary prevention with statin recommended by the guidelines.

Results
All recommended risk scores rank-ordered patients similarly, but the sensitivity of the cut-point above which statin therapy should be considered differed substantially. In younger patients (age 40-60), 62% of men and 13% of women qualified for statin therapy by ACC/AHA criteria, compared with only 2% of men and no women using the ESC criteria recommended for most non-Eastern European countries. In those 60 to 75 years of age, the ACC/AHA guidelines captured all men and 85% of women, compared with 12% and 2%, respectively, using the new ESC guideline. This guideline restricted the eligibility for primary prevention with statin substantially by reclassifying many European countries from “high-risk” to “low-risk”, whereas the eligibility was expanded in the ACC/AHA guideline and proposed NICE/UK update by lowering the decision threshold.

Conclusions
The ESC guidelines differ substantially from the ACC/AHA and proposed NICE/UK guidelines in ability to secure statin therapy to those destined for a first MI. A great opportunity for primary prevention with statin remains unexploited in Europe.

Keywords: Prevention - Cardiovascular disease - Risk assessment - SCORE - Statin
Strengths and limitations of this study

- Cohort of consecutive, contemporary patients hospitalized with a first MI, representing those seen in clinical practice today.

- Estimation of the detection rate (sensitivity) of a high-risk strategy to prevent CVD in a representative cohort of contemporary patients with failed prevention (first MI).

- A “reality check” in contemporary patients with failed prevention is easy to perform world-wide, inexpensive, and provides useful information rapidly.

- Only the detection rate (sensitivity), not the specificity, can be determined by focusing only on those who develop CVD. However, the specificity can be deduced from already existing knowledge.
INTRODUCTION
The guidelines on cardiovascular disease (CVD) prevention were revised recently in both Europe and the United States.[1-3] In 2012, the European Society of Cardiology (ESC) continued to stress the importance of using a well-calibrated version of the mortality-based SCORE (Systematic Coronary Risk Evaluation) algorithm in the primary prevention of CVD. Consequently, because of secular trends of declining CVD mortality, many European countries were reclassified from “high-risk” to “low-risk” and recommended to use the SCORE low-risk algorithm instead of the high-risk algorithm. The age-dependent risk thresholds above which primary prevention with statin should be considered were preserved. In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) released new guidelines [2,3] in which a risk calculator based on new risk equations (Pooled Cohort Equations, PCE) was introduced, together with new risk-dependent thresholds above which primary prevention with statin should be considered. More recently (February 2014), the National Institute for Health and Care Excellence (NICE) in the UK proposed to lower the threshold for statin therapy based on QRISK (scheduled for publication July 2014),[4] endorsed by the third Joint British Societies’ (JBS3) consensus recommendations for the prevention of CVD.[5] Thus, in current and draft guidelines, different criteria are used to identify people in need for primary prevention with statin.

These guidelines are endorsing the paradigm of matching the intensity of risk-reducing therapy to the absolute short-term (10-year) risk of the patient.[1-4] Although it takes 10 years of follow-up to evaluate the accuracy (calibration) of the recommended risk equations (SCORE, PCE, and QRISK), their ability to rank-order people by predicted risk and ensuring statin therapy to those at highest risk can be evaluated and compared in contemporary patients with a first CVD event. We did such a “reality check” of the new guidelines and those they replaced in patients hospitalized for a first myocardial infarction (MI).

METHODS
Study population
We reviewed the medical records of 605 consecutive patients admitted to three hospitals in Denmark with a first acute MI during 2011. Patients with preexisting CVD (n=48), diabetes (n=92), incomplete risk factor information (n=32), and statin users (n=40) were excluded, leaving 393 statin-naïve, non-diabetic, CVD-free patients with first MI. To match the age range used in the ACC/AHA guideline, we limited the study population to those 40 to 75 years of age (n=247; 162 men and 85 women). We extracted information on traditional risk factors (age, sex, smoking status, total cholesterol, high-density lipoprotein (HDL) cholesterol, and systolic blood pressure) as previously described.[6] Plasma cholesterol was measured early after admission (within the first 24 hours), and available pre-MI values were used to assess possible changes related to the acute phase of MI. The blood pressure used for estimation of risk was measured in a stable phase, either before MI (previous hospitalization or general practitioner) or after recovery from the acute phase (just before hospital discharge or first visit to the rehabilitation clinic).

Estimation of predicted risk and eligibility for statin
The guideline-recommended risk equations and web calculators used to determine predicted risk, risk factors (predictors), clinical endpoints, definitions of high-risk and recommended decision thresholds above which statin therapy should be considered are shown in Table 1 and described in the online appendix.
Table 1. Guidelines and risk equations used to estimate 10-year risk for a first cardiovascular event (primary prevention)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Risk equation</th>
<th>Derivation cohorts</th>
<th>Eligibility for statin therapy</th>
<th>Predicted outcomes</th>
</tr>
</thead>
</table>

SCORE = Systematic Coronary Risk Evaluation; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; NCEP-ATP III = National Cholesterol Education Program – Adult Treatment Panel III; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; TIA = Transient Ischemic Attack; FHS = Framingham Heart Study; CARDIA = Coronary Artery Risk Development in Young Adults Study; ARIC = Atherosclerosis Risk In Communities study; *Year baseline examination started; #Ten-year risk for the predicted outcomes;

Comparison of CVD prevention guidelines

We evaluated and compared the performance of the American and European primary prevention guidelines shown in Table 1. For each patient we calculated the absolute 10-year risk for the predicted outcomes using the recommended risk equations or calculators. In accordance with the SCORE risk charts [1] and the online risk calculator HeartScore,[17] the age-dependent risk was capped at age 65 when estimating risk using the SCORE algorithms. The guidelines were compared in three steps as described in the online appendix.

Ethical considerations

The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.
RESULTS
Baseline characteristics of the study population are shown in Table 2. We identified 393 statin-naïve, non-diabetic, CVD-free patients with first MI of whom 13 below age 40 and 133 above age 75 were excluded, leaving 247 patients (162 men, 85 women) for the present study.

Table 2. Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (40-75 years)</th>
<th>40-60 years</th>
<th>61-75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients no.</td>
<td>247</td>
<td>96 (39%)</td>
<td>151 (61%)</td>
</tr>
<tr>
<td>Age</td>
<td>61.9 (9.3)</td>
<td>51.7 (4.9)</td>
<td>68.4 (4.2)</td>
</tr>
<tr>
<td>Men</td>
<td>162 (66%)</td>
<td>65 (68%)</td>
<td>97 (64%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>137 (19.8)</td>
<td>131 (19.0)</td>
<td>140 (21.4)</td>
</tr>
<tr>
<td>Plasma parameters, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.3 (1.0)</td>
<td>5.4 (1.0)</td>
<td>5.2 (1.0)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>3.3 (0.9)</td>
<td>3.4 (0.9)</td>
<td>3.3 (0.9)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.3 (0.4)</td>
<td>1.2 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>53</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>Blood pressure lowering therapy, %</td>
<td>30</td>
<td>21</td>
<td>35</td>
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Continuous variables: mean (SD)

2013 ACC/AHA versus ATP III
Ranking patients with first MI by predicted risk estimated by PCE (used in the new ACC/AHA risk calculator) and the previously recommended ATP III risk calculator correlated strongly (Figure 1). PCE risk ≥7.5%, which is a strong/class I recommendation for statin therapy, corresponded to ATP III risk ≥9.5% in men and ≥4.1% in women and, compared with ATP III risk ≥10%, captured nearly the same men but substantially more women with first MI (Figure 1 and 2, Table 3).

Table 3. Risk equivalent to PCE 7.5% and 5% determined by other risk equations*

<table>
<thead>
<tr>
<th></th>
<th>PCE 2013</th>
<th>ATP III 2002</th>
<th>QRISK2 2013</th>
<th>SCORE+HDL High-Risk</th>
<th>SCORE+HDL Low-Risk</th>
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<tr>
<td>Men</td>
<td>7.5</td>
<td>9.5</td>
<td>7.0</td>
<td>2.9</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6.3</td>
<td>5.4</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Women</td>
<td>7.5</td>
<td>4.1</td>
<td>10.1</td>
<td>3.6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3.0</td>
<td>6.8</td>
<td>2.1</td>
<td>1.2</td>
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</table>

*Based on linear regression of those with PCE risk <7.5% (Figure 1 and 3-5).
2013 ACC/AHA versus 2010 and draft 2014 NICE/UK

Ranking patients with first MI by predicted risk estimated by PCE and the QRISK risk calculator correlated strongly (Figure 3). A PCE risk of 7.5% corresponded to a risk of 7.0% in men and 10.1% in women estimated by QRISK (Table 3).

Compared with the ACC/AHA guidelines, much fewer patients with first MI qualified for primary prevention with statin using the 2010 NICE/UK guidelines (Figure 2). Below age 60, only 2% of men and no women qualified for treatment by the UK guideline (QRISK ≥20%), whereas 62% of men and 13% of women qualified by the ACC/AHA guideline (PCE ≥7.5%). However, the eligibility for statin was nearly similar with UK and US guidelines if the treatment threshold was lowered from QRISK 20% to 10% as recently proposed by the 2014 draft update of NICE/UK guidelines (Figure 2 and 3).[4]

2013 ACC/AHA versus 2012 ESC

Ranking patients with first MI by predicted risk estimated by PCE and SCORE+HDL high-risk equations correlated strongly (Figure 4). A PCE risk of 7.5% corresponded to a risk of 2.9% in men and 3.6% in women estimated by the SCORE+HDL high-risk equation (Table 3).

The 2013 ACC/AHA guideline captured double as many men and four times more women with first MI compared with a common interpretation of the 2012 ESC guideline (SCORE ≥5% below age 60 and ≥10% above 60) (Figure 2 and 4). This contrasting performance was accentuated with the SCORE low-risk equation recommended for use in Denmark and most other non-Eastern European countries (Figure 5). PCE 7.5% corresponded to SCORE 1.5% in men and 2.0% in women (Table 3). Below age 60, only 2% of men and no women with first MI qualified for statin therapy by the ESC guideline (SCORE ≥5%), whereas 62% of men and 13% of women qualified for a class I recommendation by the ACC/AHA guideline (Figure 2). Above age 60, 12% of men and 2% of women qualified for treatment in Europe (SCORE ≥10%), in contrast to all men and 85% of women in the US.

ESC 2012 versus ESC 2003 and 2007

Predicted risk estimated by the SCORE+HDL high-risk and low-risk equations correlated perfectly (see online supplementary figure). Predicted risk was 1.7 times higher in men and 1.9 times higher in women when estimated by the high-risk equation compared with the low-risk equation. Thus, 5% risk determined by the high-risk equation recommended until 2012 corresponded to only 2.9% risk in men and 2.6% risk in women determined by the low-risk equation now recommended. Consequently, 85 of 162 males (52%) and 27 of 85 females (32%) with a first MI who would have been eligible for primary prevention with statin under the previous ESC guidelines lost their eligibility when Denmark (and many other European countries) was reclassified from a “high-risk” to a “low-risk” country in the new guidelines (Figure 2 and online supplementary figure).[1]

DISCUSSION

A reality check of guidelines on CVD prevention in patients with a first MI revealed that many more patients would have been eligible for primary prevention with statin by following the 2013 ACC/AHA guideline compared with the 2012 ESC and 2010 NICE guidelines. The use of statin was liberalized in the US in 2013, but indirectly restricted in many European countries in 2012 by recommending the SCORE low-risk equation instead of the high-risk equation.[1] With the low-risk equation, only 13 of 162 men (8%) and 1 of 85 women (1%) with a first MI would have qualified for primary prevention with statin. Lowering the treatment threshold as recommended by the 2014 draft update of the NICE/UK guideline [4] will leave ESC alone with increasingly restrictive recommendations on primary prevention with statin.

As expected, ranking patients by predicted risk estimated with different multifactorial risk equations correlated strongly, indicating that their ability to discriminate cases from non-cases is similar for practical...
purposes.[18,19] Thus, the clinical performance depends critically on how accurate risk is estimated (calibration) and the decision thresholds recommended in the respective guidelines.

**US guideline**

Immediately after release of the 2013 ACC/AHA guideline, the new PCE-based risk model was accused of being miscalibrated because it systematically overestimated risk in certain external validation cohorts,[20] which could lead to massive overtreatment with statin.[21] A possible overestimation of risk in contemporary populations was realized in the guideline document,[2] and alternative explanations for the unexpected results obtained in the validation cohorts were provided.[22] In our patients with a first MI, ≥7.5% risk estimated by the new risk equation captured the same proportion of patients as ≥9.5% risk in men and ≥4.1% in women estimated by the prior ATP III risk equation. Because the clinical outcomes predicted by PCE are more numerous than those predicted with ATP III by including stroke in addition to hard CHD, PCE in fact underestimated risk in men compared with ATP III. Because ischemic stroke is nearly as common as MI in women,[23] PCE risk ≥7.5% seems commensurate with ATP III risk ≥4.1%. Thus, compared with the risk model it replaced, the new PCE-based risk model does not seem to overestimate risk at or below the new risk thresholds for statin therapy. Recently, PCE was found to be well-calibrated in a contemporary US cohort,[24] and PCE performed reasonably well (not inferior to SCORE) in a UK “low-risk” population.[25]

If the new guidelines give rise to wider use of statin for primary prevention of CVD, a plausible explanation is that the bar for treatment deliberately was lowered substantially by these guidelines.[22,26] The cut-point for treatment was established based on risk-benefit considerations alone,[2,3] cost-effectiveness of fixed-dose not target driven statin therapy was not questioned.[26] The new ACC/AHA guidelines are expected to increase the number of people eligible for primary prevention with statin in the US substantially.[27]

**European guidelines**

The SCORE-based ESC guidelines have always stressed that the indication for drug therapy should be based on an accurate estimate of absolute risk for fatal CVD, taking age into consideration.[1] A paradoxical consequence is that when SCORE is recalibrated to fit a lower CVD mortality, it becomes harder to get the treatment that contributed to the lower mortality. Thus, the 2012 ESC guideline indirectly restricted the use of risk-reducing statin by reclassifying many high-income European countries from “high-risk” to “low-risk” and recommending the more accurately calibrated SCORE low-risk equations instead of the high-risk equations.[1] Twenty-five European countries are now classified as “low-risk”, compared with only eight in 2007.[1] With preserved age- and risk-dependent eligibility for statin therapy, our data show that the low-risk equations capture very few people destined for a first MI (Figure 2). Obviously, the current mortality-based decision thresholds are not geared to prevent the large burden of nonfatal CVD and still increasing health care costs.

 QRISK predicts an expanded CVD endpoint compared with PCE (PCE endpoints + angina and transient ischemic attack) and, consequently, risks estimated by the QRISK2-2013 risk calculator should be higher than those estimated by the PCE-based risk calculator. Nonetheless, they don't differ much (Figure 3, Table 3), which indicates that at least one of these risk models is miscalibrated in contemporary patients. Today, substantially more people would qualify for primary prevention with statin based on PCE ≥7.5% (recommended in US) compared to QRISK ≥20% (recommended in UK) (Figure 2). However, lowering the treatment threshold from QRISK 20% to 10%, as proposed by NICE in the February 2014 draft update,[4] will bring the guideline in UK close to the 2013 ACC/AHA guideline.

**Contrasting recommendations after age 60**

The 2013 ACC/AHA guideline recommends neither for nor against statin therapy for primary prevention in non-diabetic people above 75.[3] The NICE guideline recommends that people aged 75 or older should be considered for statin treatment, particularly those who smoke or have high blood pressure.[9] The new recommendation (number 55) in the proposed NICE update reads as follows: “Consider atorvastatin 20 mg for people older than 85 years because they are likely to benefit from statin treatment”. [4] In contrast, the
ESC guideline recommends a higher bar for statin treatment already after age 60 and provides SCORE risk charts only up to age 65.[1] Beyond age 65, the ESC guidelines provide no guidance on how to assess risk. It is possible, but not recommended, to enter age up to 100 years in the online risk calculator, HeartScore, but the age-dependent risk is capped at age 65.[17] So, in clinical practice, very few elderly people in “low-risk” countries will qualify for primary prevention with statin if the ESC guidelines are used as intended. In an elderly population, a high eligibility for statin therapy was recently reported by calculating the risk by entering the actual age into the underlying SCORE equations and thus ignoring how SCORE is used clinically where the age-dependent risk is capped at age 65.[28]

The future: reality check in contemporary patients with a first CVD event

When treatment decisions are based on absolute 10-year risk for developing CVD, accurate estimation of 10-year risk is essential to treat people as intended. It is problematic for several reasons. Predicting risk based on historical and potentially outdated data is risky in populations where lifestyle, medicalisation, morbidity and mortality are changing rapidly.[20-22,29] A contemporary (sub)population against which to update (recalibrate) a risk score is often lacking.[18,22] Applicable “natural history” cohorts are vanishing because of wider use of risk-reducing medications already at baseline and during follow-up.[22,24] Generalisability may be questioned because of non-reproducible or inapplicable endpoints or uncertain ascertainment and adjudication.[2,10,24] Overall, a primary prevention strategy based on absolute risk is not always feasible, illustrated by the suboptimal guidance to ethnic groups other than non-Hispanic Whites and African Americans in the new ACC/AHA guidelines.[2,3]

Alternatively and/or complementary, a reality check in contemporary patients with a first MI can reveal how a high-risk strategy performs in clinical practice. First, the sensitivity of the decision thresholds can be assessed. Second, because the discriminative performance of traditional risk scores vary little across populations,[18,19] an estimate of the corresponding specificity can be deduced from a representative receiver-operating characteristic curve. Third, the proportion of first MI prevented by statin therapy can be estimated. In the present study, 40 (9%) of 433 CVD-free, non-diabetic patients used statin before their first MI. Assuming statin therapy reduces the risk by 30%, without statin we would have expected only 17 more first AMI cases (40/0.7 = 57), indicating that the current use of statin in this population prevented very few first AMIs (~4%). Finally, a reality check is easy to perform world-wide, inexpensive, and provides useful information rapidly.

Limitations

Our study has important strengths. This analysis was performed in a representative cohort of first MI cases, with an age- and sex-distribution routinely seen in clinical practice. Thus, the actual performance of current guidelines on CVD prevention is provided. However, some potential limitations need to be addressed. A reality check of primary prevention guidelines requires that predictors for a first atherosclerotic event can be assessed after the event. They can with the approach used in this study. First, the strongest predictors of risk (age, sex, and smoking) can always be determined after as well as before the event, and the impact of small changes in cholesterol and blood pressure on multi-factorial risk assessment is critical only near the risk-based decision threshold. Plasma cholesterol was measured early after admission (within the first 24 hours), which today is accepted to represent baseline values;[30] plasma cholesterol was indeed only 5% lower in the 181 patients in whom a paired pre-MI value was available for comparison. The blood pressure used for estimation of predicted risk was obtained in a stable phase, either before MI (previous hospitalization or general practitioner) or after recovery from the acute phase (just before hospital discharge or first visit to the rehabilitation clinic). The blood pressure was similar before and after MI in 99 patients in whom paired values were available for comparison.[6] Only few non-diabetic, CVD-free patients used statin before the first MI (n=40, 9%), and they were excluded. In patients with a first MI, only the detection rate (sensitivity) of decision thresholds can be determined, not the specificity. However, if a decision threshold captures only a minority of those it was intended to identify, the appropriateness of the recommended strategy needs to be reconsidered.
Conclusion
The 2012 ESC and 2013 ACC/AHA guidelines differ substantially in their ability to secure statin therapy to those destined for a first MI. In Europe, with the exception of UK, eligibility for primary prevention with statin is becoming increasingly restricted in non-Eastern European countries by updating only the mortality-based SCORE equations, not the risk thresholds on which treatment decisions are based. In the US and possibly UK, a treatment threshold based on risk-benefit [3] and cost-effectiveness [4] considerations has now been defined, leading to a wider eligibility for statin therapy.

Acknowledgements
We thank Ole May, Ole Gotzsche, Helle Kanstrup, Jette Bertelsen, Helle K. Jensen, Willemijn Comuth and Kim Sivesgaard for their assistance in collecting information on traditional risk factors from the medical records.

Contributors
Both authors contributed equally to this study, including study design, data analysis, interpretation of the results, drafting the manuscript, and final approval of the manuscript. Both authors take full responsibility for the work.

Funding
This work was supported by the Institute of Clinical Medicine at Aarhus University, Denmark.

Competing interests
None

Ethics approval
The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.

Data sharing statement
No additional data are available.
REFERENCES


FIGURE LEGENDS

Figure 1. Eligibility for statin therapy by ACC/AHA versus ATP III.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the Adult Treatment Panel III (ATP III) risk calculator correlated strongly (Spearman’s rho 0.86 in men and 0.82 in women; p<0.0001). Compared with ATP III risk ≥10%, PCE risk ≥7.5% captured nearly the same men but substantially more women with first MI. The ATP III risk calculator only provides whole numbers, and the absolute risk is capped at 30%. For PCE <7.5%, y = 1.261*x + 0.00026 in men, and y = 0.4476*x + 0.7274 in women.

Figure 2. Proportion (%) of patients with first myocardial infarction who would have been eligible for primary prevention with statin.
The SCORE Low-Risk equation is recommended for use in Denmark and 24 other European countries with a relatively low cardiovascular mortality. The exact values and guideline-defined decision thresholds behind this bar diagram are shown in the online appendix (see supplementary table).

Figure 3. Eligibility for statin therapy by ACC/AHA versus NICE/UK.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the QRISK2-2013 risk equation correlated strongly (Spearman’s rho 0.94 in men and 0.97 in women; p<0.0001). Compared with PCE risk ≥7.5%, QRISK ≥20% (indication for statin therapy in 2010 NICE/UK) identified much fewer patients with first MI, whereas QRISK ≥10% (indication for statin in draft 2014 update) identified nearly the same patients, especially among women. For PCE <7.5%, y = 0.6385*x + 2.171 in men, and y = 1.308*x + 0.2708 in women.

Figure 4. Eligibility for statin therapy by ACC/AHA versus ESC “high-risk” countries.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the SCORE+HDL High-Risk equation correlated strongly (Spearman’s rho 0.89 in men and 0.84 in women; p<0.0001). The PCE-defined treatment threshold of 7.5% captured double as many men and four times more women with first MI compared with the SCORE-defined treatment thresholds of 5% below age 60 and 10% above 60. For PCE <7.5%, y = 0.3514*x + 0.3034 in men, and y = 0.6065*x + 0.9550 in women.

Figure 5. Eligibility for statin therapy by ACC/AHA versus ESC “low-risk” countries.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and SCORE+HDL Low-Risk equation correlated strongly (Spearman’s rho 0.91 in men and 0.83 in women; p<0.0001). Only 13 of 162 men (8%) and 1 of 85 women (1%) with first MI qualified for primary prevention with statin using the SCORE-defined treatment threshold of 5% below age 60 and 10% above 60. For PCE <7.5%, y=0.1519*x+0.3258 in men, and y=0.3203*x-0.4519 in women.
Figure 1. Eligibility for statin therapy by ACC/AHA versus ATP III.

Predicted risk estimated by the Pooled Cohort Equations (PCE) and the Adult Treatment Panel III (ATP III) risk calculator correlated strongly (Spearman’s rho 0.86 in men and 0.82 in women; p<0.0001). Compared with ATP III risk ≥10%, PCE risk ≥7.5% captured nearly the same men but substantially more women with first MI. The ATP III risk calculator only provides whole numbers, and the absolute risk is capped at 30%.

For PCE <7.5%, \( y = 1.261 \times x + 0.00026 \) in men, and \( y = 0.4476 \times x + 0.7274 \) in women.
Figure 2. Proportion (%) of patients with first myocardial infarction who would have been eligible for primary prevention with statin.

The SCORE Low-Risk equation is recommended for use in Denmark and 24 other European countries with a relatively low cardiovascular mortality. The exact values and guideline-defined decision thresholds behind this bar diagram are shown in the online appendix (see supplementary table).
Figure 3. Eligibility for statin therapy by ACC/AHA versus NICE/UK.

Predicted risk estimated by the Pooled Cohort Equations (PCE) and the QRISK2-2013 risk equation correlated strongly (Spearman’s rho 0.94 in men and 0.97 in women; p<0.0001). Compared with PCE risk ≥7.5%, QRISK ≥20% (indication for statin therapy in 2010 NICE/UK) identified much fewer patients with first MI, whereas QRISK ≥10% (indication for statin in draft 2014 update) identified nearly the same patients, especially among women.

For PCE <7.5%, $y = 0.6385x + 2.171$ in men, and $y = 1.308x + 0.2708$ in women.

278x125mm (300 x 300 DPI)
Figure 4. Eligibility for statin therapy by ACC/AHA versus ESC "high-risk" countries.

Predicted risk estimated by the Pooled Cohort Equations (PCE) and the SCORE+HDL High-Risk equation correlated strongly (Spearman’s rho 0.89 in men and 0.84 in women; p<0.0001). The PCE-defined treatment threshold of 7.5% captured double as many men and four times more women with first MI compared with the SCORE-defined treatment thresholds of 5% below age 60 and 10% above 60.

For PCE <7.5%, y = 0.3514*x + 0.3034 in men, and y = 0.6065*x + 0.9550 in women.

275x131mm (300 x 300 DPI)
Figure 5. Eligibility for statin therapy by ACC/AHA versus ESC “low-risk” countries.

Predicted risk estimated by the Pooled Cohort Equations (PCE) and SCORE+HDL Low-Risk equation correlated strongly (Spearman’s rho 0.91 in men and 0.83 in women; p<0.0001). Only 13 of 162 men (8%) and 1 of 85 women (1%) with first MI qualified for primary prevention with statin using the SCORE-defined treatment threshold of 5% below age 60 and 10% above 60.

For PCE <7.5%, $y=0.1519x+0.3258$ in men, and $y=0.3203x-0.4519$ in women.

277x126mm (300 x 300 DPI)
Online Appendix

Reality check of high-risk strategies for primary prevention of cardiovascular disease in Europe and United States

Martin B. Mortensen and Erling Falk

Atherosclerosis Research Unit, Department of Cardiology, Aarhus University Hospital, 8200 Aarhus, Denmark

Supplementary Material

- Supplementary Methods
- Supplementary Table
- Supplementary Figure
Supplementary Methods

Estimation of predicted risk and eligibility for statin

The guideline-recommended risk equations and web calculators used to determine predicted risk, risk factors (predictors), clinical endpoints, definitions of high-risk and recommended decision thresholds above which statin therapy should be considered are shown in Table 1 in the printed article and described below.

The 2012 ESC recommendations for primary prevention are based on the SCORE model introduced in 2003 that predicts 10-year risk for fatal CVD in people 40 to 65 years of age.[1] Two standard SCORE risk charts/equations are available, one for countries with a high incidence of fatal CVD, the other for countries with a low incidence. Denmark, together with many other European countries, was reclassified from “high-risk” to “low-risk” in 2012 and recommended to use the SCORE low-risk equation instead of the high-risk equation. As another novelty, HDL-adjusted risk estimates became available in 2012, either as risk charts or the electronic version of SCORE. HeartScore.[2] HeartScore allows entry of age up to 100 years but the age-dependent risk is capped at age 65. The LDL-C dependent eligibility for statin therapy is based on both estimated 10-year risk and age, expressed in the following way: “In general, those with a risk of CVD death of ≥5% qualify for intensive advice, and may benefit from drug treatment. At risk levels >10%, drug treatment is more frequently required. In persons older than 60, these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other cardiovascular risk factor levels are ‘normal’.[1] While no universally applicable risk threshold for statin therapy is given, a common interpretation is that statin therapy should be considered at SCORE ≥5% (defined as high risk) below age 60 and ≥10% (defined as very high risk) above 60.

The 2013 ACC/AHA recommendations for primary prevention are based on the newly developed PCE that predict 10-year risk for atherosclerotic CVD (ASCVD) defined as nonfatal MI, CHD death, and fatal and nonfatal stroke.[3,4] The downloadable PCE-based risk calculator provides race- and sex-specific 10-year and lifetime risks of ASCVD in nonhispanic Whites and nonHispanic African Americans.[5] For other ethnic groups, use of the sex-specific estimates calculated for nonhispanic Whites may be considered (expert opinion/IIB recommendation).[4] In adults 40 to 75 years of age, eligibility for statin therapy is PCE ≥7.5% (strong/class I recommendation) and 5% to <7.5% (weak/class IIa recommendation).[4]

The 2013 ACC/AHA guideline replaced the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program.[6,7] ATP III-based risk assessment used a Framingham-derived risk equation that predicted 10-year risk for hard coronary heart disease (CHD) defined as nonfatal MI and fatal CHD. The web-based risk calculator is still available.[8] The treatment algorithm for primary prevention with statin was complicated, depending on number of risk factors, low-density lipoprotein cholesterol (LDL-C) levels, and estimated 10-year risk (>20%: nearly unconditional treatment; 10-20%: conditional treatment).[6,7]

The 2010 revision of the NICE (National Institute for Health and Care Excellence) guideline recommends to estimate 10-year risk for CVD, defined by QRISK as CHD (angina and MI), stroke, and transient ischemic attack.[9,10] The latest version of the risk calculator, QRISK®-2013, was used for this study.[11] When QRISK2 is used outside UK, an average value for social deprivation (UK postcode) is used to calculate the score. For primary prevention in people aged 40-74, statin therapy is recommended at QRISK ≥20% (defined as high risk). People aged 75 or older are at increased risk for CVD and should be considered for statin treatment, particularly those who smoke or have high blood pressure.[9] February 2014, a draft guideline from NICE proposes to lower the threshold for primary prevention with statin from 20% to 10% estimated by the QRISK2 risk calculator.[12] endorsed by JBS3.[13]

Comparison of CVD prevention guidelines
We evaluated and compared the performance of the American and European primary prevention guidelines shown in Table 1 in the printed article. For each patient we calculated the absolute 10-year risk for the...
predicted outcomes using the recommended risk equations or calculators. In accordance with the SCORE risk charts [1] and the online risk calculator HeartScore,[2] the age-dependent risk was capped at age 65 when estimating risk using the SCORE algorithms. The guidelines were compared in three steps as described below.

First, we assessed the concordance in CVD risk characterization between the PCE and the four other risk equations/calculators (ATP III, QRISK2, SCORE+HDL low-risk and SCORE+HDL high-risk) by computing the Spearman rank-order correlation coefficients (Spearman’s rho). Secondly, the new American ACC/AHA risk thresholds of 5% and 7.5% were translated to risks estimated by the other risk equations/calculators. The risk values estimated by ATP III, QRISK2 and SCORE+HDL that corresponded to PCE risks of 5% and 7.5% were determined from sex-specific linear regression equations derived from pairwise comparisons of predicted risk in persons with a PCE risk <7.5%. Finally, we determined the proportion of patients with a first MI who would have been eligible for primary prevention with statin based on recommendations in the former and the new American and European guidelines. Men and women were analyzed separately, and stratified by pre-specified age groups (40 to 60 years and 60 to 75 years).

REFERENCES


2. ESC HeartScore risk calculator. Available at: http://www.heartscore.org


5. ACC/AHA atherosclerotic cardiovascular disease risk calculator. Available at: http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp


Supplementary Table

Supplementary Table. Proportion of patients (detection rate) with first MI who had a predicted risk of atherosclerotic CVD above which primary prevention with statin should be considered.

<table>
<thead>
<tr>
<th>Guideline Algorithm</th>
<th>Risk threshold</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40-60 years of age</td>
<td>60-75 years of age</td>
</tr>
<tr>
<td></td>
<td>Men n=65</td>
<td>Women n=31</td>
</tr>
<tr>
<td>2012 ESC European Guideline SCORE+HDL Low-Risk</td>
<td>5%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>2012 ESC European Guideline SCORE+HDL High-Risk</td>
<td>5%</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>2013 ACC/AHA Pooled Cohort Equations/White</td>
<td>5%</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>7.5%</td>
<td>62</td>
</tr>
<tr>
<td>Adult Treatment Panel III Modified Framingham Equation</td>
<td>10%</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>12</td>
</tr>
<tr>
<td>2010 &amp; 2014 NICE/UK QRISK2-2013/White</td>
<td>10%</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>2</td>
</tr>
</tbody>
</table>

1Statin therapy should be considered at SCORE ≥5% below age 60 and ≥10% above 60.[1]
2Recommendations for statin therapy are 10-year risk ≥7.5% (strong/class I) and 5% to <7.5% (weak/class IIa).[2]
3Recommendations for statin therapy depending on risk factors, cholesterol level, and 10-year risk >20% (~unconditional treatment) and 10-20% (conditional treatment).[3]
4,5Indication for statin therapy is 10-year risk ≥20% [4] but in Feb 2014 proposed to be lowered to ≥10%.[5]

REFERENCES

Available at: http://eurheartj.oxfordjournals.org/content/33/13/1635.full.pdf+html

Available at: http://www.sciencedirect.com/science/article/pii/S0735109713060282


Supplementary Figure. Eligibility for statin therapy by high-risk versus low-risk SCORE equation.

Predicted risk estimated by the High-Risk and Low-Risk SCORE equations correlated perfectly (Spearman’s rho ≥0.99; $R^2 = 0.99; p<0.0001$). The High-Risk equation consistently overestimates risk compared with the Low-Risk equation. Classification based on the guideline-defined decision thresholds of 5% and 10% was discordant in 85 of 162 males (52%) and 27 of 85 females (32%), with potential loss of indication for statin therapy by recalibration of SCORE to fit a lower mortality of cardiovascular disease.

ESC: European Society of Cardiology.
Real-life evaluation of European and American high-risk strategies for primary prevention of cardiovascular disease in patients with first myocardial infarction

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<td>15-Aug-2014</td>
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</table>
Real-life evaluation of European and American high-risk strategies for primary prevention of cardiovascular disease in patients with first myocardial infarction

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Phone: +45 51355929

Keywords: Prevention - Cardiovascular disease - Risk assessment - SCORE - Statin
ABSTRACT

Objective
To determine the detection rate (sensitivity) of the high-risk strategy recommended in the European (ESC and NICE/UK) and American (ACC/AHA) guidelines on cardiovascular disease (CVD) prevention. In particular, to evaluate the ability to ensure statin therapy to contemporary Europeans destined for a first myocardial infarction (MI).

Design
393 consecutive statin-naive, non-diabetic, CVD-free patients hospitalized for a first MI, 247 of whom were 40 to 75 years of age. We assumed they had undergone a health check the day before their MI and estimated the predicted risk.

Primary outcome
Sensitivity of the risk-based eligibility for primary prevention with statins recommended by the guidelines.

Results
All recommended risk scores rank-ordered patients similarly, but the sensitivity of the cut-point above which statin therapy should be considered differed substantially. In younger patients (age 40-60), 62% of men and 13% of women qualified for statin therapy by ACC/AHA criteria, compared with only 2% of men and no women using the ESC criteria recommended for most non-Eastern European countries. In those 60 to 75 years of age, the ACC/AHA guidelines captured all men and 85% of women, compared with 12% and 2%, respectively, using the new ESC guideline. This guideline restricted the eligibility for primary prevention with statins substantially by reclassifying many European countries from “high-risk” to “low-risk”, whereas the eligibility was expanded in the ACC/AHA and the new NICE/UK guidelines by lowering the decision threshold.

Conclusions
The 2012 ESC guidelines differ substantially from the 2013 ACC/AHA and 2014 NICE/UK guidelines in ability to secure statin therapy to those destined for a first MI. A great opportunity for primary prevention with statins remains unexploited in Europe.
Strengths and limitations of this study

- Cohort of consecutive, contemporary patients hospitalized with a first MI, representing those seen in clinical practice today.

- Estimation of the detection rate (sensitivity) of a high-risk strategy to prevent MI in a representative cohort of contemporary, non-diabetic patients with failed prevention (first MI).

- A “reality check” of a high-risk strategy in contemporary patients with failed prevention is easy to perform world-wide, inexpensive, and provides useful information rapidly.

- Only the detection rate (sensitivity), not the specificity, can be determined by focusing only on those who develop CVD.
INTRODUCTION
The guidelines on cardiovascular disease (CVD) prevention were revised recently in both Europe and the
United States.[1-4] In 2012, the European Society of Cardiology (ESC) continued to stress the importance of
using a well-calibrated version of the mortality-based SCORE (Systematic Coronary Risk Evaluation)
algorithm in the primary prevention of CVD. Consequently, because of secular trends of declining CVD
mortality, many European countries were reclassified from “high-risk” to “low-risk” and recommended to
use the SCORE low-risk algorithm instead of the high-risk algorithm. The age-dependent risk thresholds
above which primary prevention with statins should be considered were preserved. In 2013, the American
College of Cardiology and the American Heart Association (ACC/AHA) released new guidelines [2,3] in
which a risk calculator based on new risk equations (Pooled Cohort Equations, PCE) was introduced,
together with new risk-dependent thresholds above which primary prevention with statins should be
considered. In 2014, the National Institute for Health and Care Excellence (NICE) in the UK recommended
to halve the risk-based threshold for primary prevention with statins based on QRISK,[4] endorsed by the
third Joint British Societies’ (JBS3) consensus recommendations for the prevention of CVD.[5] Thus, in
current European and American guidelines, different criteria are used to identify people in need for primary
prevention with statins.

These guidelines are endorsing the paradigm of matching the intensity of risk-reducing therapy to the
absolute 10-year risk of the patient.[1-4] Although it takes many years of follow-up to evaluate how accurate
the recommended risk equations (SCORE, PCE, and QRISK) are calibrated, their ability to rank-order
people by predicted risk and ensuring statin therapy to those at highest risk can be evaluated and compared in
contemporary patients with a first CVD event. We did such a “reality check” of the new guidelines and those
they replaced in patients hospitalized for a first myocardial infarction (MI).

METHODS
Study population
We reviewed the medical records of 605 consecutive patients admitted to three hospitals in Denmark
(departments of cardiology/medicine at Aarhus University Hospital and the Regional Hospitals in Herning
and Randers) with a first acute MI between January 1 through December 31 in 2011. The universal definition
of MI is implemented in Denmark,[6] and the patients were identified via hospital registers using ICD-10
codes I21.0 through I21.9. Patients with preexisting CVD (n=48), diabetes (n=92), incomplete risk factor
information (n=32), and statin users (n=40) were excluded (diabetic patients do not belong to the target
population for risk assessment defined by the ESC and ATP III guidelines), leaving 393 statin-naïve, non-
diabetic, CVD-free patients with first MI. To match the age range used in the ACC/AHA guideline, we
limited the study population to those 40 to 75 years of age (n=247; 162 men and 85 women). We extracted
information on traditional risk factors (age, sex, smoking status, total cholesterol, high-density lipoprotein
(HDL) cholesterol, and systolic blood pressure) as previously described.[7] Plasma cholesterol was measured
early after admission (within the first 24 hours), and available pre-MI values were used to assess possible
changes related to the acute phase of MI. The blood pressure used for estimation of risk was measured in a
stable phase, either before MI (previous hospitalization or general practitioner) or after recovery from the
acute phase (just before hospital discharge or first visit to the rehabilitation clinic).

Estimation of predicted risk and eligibility for statin
The guideline-recommended risk equations and web calculators used to determine predicted risk, risk factors
(predictors), clinical endpoints, definitions of high-risk and recommended decision thresholds above which
statin therapy should be considered are shown in Table 1 and described in the online appendix.
Table 1. Guidelines and risk equations used to estimate 10-year risk for a first cardiovascular event (primary prevention)

<table>
<thead>
<tr>
<th>Guideline Risk equation</th>
<th>Derivation cohorts</th>
<th>Eligibility for statin therapy</th>
<th>Predicted outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 ACC/AHA [3]</td>
<td>FHS: 1948 [11,12]</td>
<td>≥7.5% (strong/class I) 5% to &lt;7.5% (weak/class IIa)</td>
<td>ASCVD: nonfatal MI, fatal CHD, fatal and nonfatal stroke</td>
</tr>
</tbody>
</table>

SCORE = Systematic CORonary Risk Evaluation; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; NCEP-ATP III = National Cholesterol Education Program – Adult Treatment Panel III; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; TIA = Transient Ischemic Attack; CHS = Cardiovascular Health Study; FHS = Framingham Heart Study; CARDIA = Coronary Artery Risk Development in Young Adults Study; ARIC = Atherosclerosis Risk In Communities study; *Year baseline examination started; Ten5year risk for the predicted outcomes; 

Comparison of CVD prevention guidelines
We evaluated and compared the performance of the American and European primary prevention guidelines shown in Table 1. For each patient we calculated the absolute 10-year risk for the predicted outcomes using the recommended risk equations or calculators. In accordance with the SCORE risk charts [1] and the online risk calculator HeartScore,[17] the age-dependent risk was capped at age 65 when estimating risk using the SCORE algorithms. The guidelines were compared in three steps as described in the online appendix.

Ethical considerations
The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.
RESULTS
Baseline characteristics of the study population are shown in Table 2. We identified 393 statin-naïve, non-diabetic, CVD-free patients with first MI of whom 13 below age 40 and 133 above age 75 were excluded, leaving 247 patients (162 men, 85 women) for the present study.

Table 2. Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (40-75 years)</th>
<th>40-60 years</th>
<th>61-75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients no.</td>
<td>247</td>
<td>96 (39%)</td>
<td>151 (61%)</td>
</tr>
<tr>
<td>Age</td>
<td>61.9 (9.3)</td>
<td>51.7 (4.9)</td>
<td>68.4 (4.2)</td>
</tr>
<tr>
<td>Men</td>
<td>162 (66%)</td>
<td>65 (68%)</td>
<td>97 (64%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>137 (19.8)</td>
<td>131 (19.0)</td>
<td>140 (21.4)</td>
</tr>
<tr>
<td>Plasma parameters, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.3 (1.0)</td>
<td>5.4 (1.0)</td>
<td>5.2 (1.0)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>3.3 (0.9)</td>
<td>3.4 (0.9)</td>
<td>3.3 (0.9)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.3 (0.4)</td>
<td>1.2 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>53</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>Blood pressure lowering therapy, %</td>
<td>30</td>
<td>21</td>
<td>35</td>
</tr>
</tbody>
</table>

Continuous variables: mean (SD). LDL = low-density lipoprotein; HDL = high-density lipoprotein;

2013 ACC/AHA versus ATP III
Ranking patients with first MI by predicted risk estimated by PCE (used in the new ACC/AHA risk calculator) and the previously recommended ATP III risk calculator correlated strongly (Figure 1). PCE risk ≥7.5%, which is a strong/class I recommendation for statin therapy, corresponded to ATP III risk ≥9.5% in men and ≥4.1% in women and, compared with ATP III risk ≥10%, captured nearly the same men but substantially more women with first MI (Figure 1 and 2, Table 3).

Table 3. Risk equivalent to PCE 7.5% and 5% determined by other risk equations*

<table>
<thead>
<tr>
<th></th>
<th>Predicted 10-year risk of diverse CVD outcomes (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCE 2013</td>
<td>ATP III 2002</td>
<td>QRISK2 2013</td>
<td>SCORE+HDL High-Risk</td>
<td>SCORE+HDL Low-Risk</td>
</tr>
<tr>
<td>Men</td>
<td>7.5</td>
<td>9.5</td>
<td>7.0</td>
<td>2.9</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6.3</td>
<td>5.4</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Women</td>
<td>7.5</td>
<td>4.1</td>
<td>10.1</td>
<td>3.6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3.0</td>
<td>6.8</td>
<td>2.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Based on linear regression of those with PCE risk <7.5% (Figure 1 and 3-5). ATP III = Adult Treatment Panel III; CVD = cardiovascular disease; HDL = high-density lipoprotein; PCE = Pooled Cohort Equations; SCORE = Systematic COronary Risk Evaluation;
2013 ACC/AHA versus 2014 NICE/UK
Ranking patients with first MI by predicted risk estimated by PCE and the QRISK risk calculator correlated strongly (Figure 3). A PCE risk of 7.5% corresponded to a risk of 7.0% in men and 10.1% in women estimated by QRISK (Table 3). Thus, with the 2014 NICE/UK recommendation to lower the QRISK-based threshold for statin therapy from 20% to 10%, the eligibility for primary prevention with statins is nearly similar in the US and the UK (Figure 2 and 3).

2013 ACC/AHA versus 2012 ESC
Ranking patients with first MI by predicted risk estimated by PCE and SCORE+HDL high-risk equations correlated strongly (Figure 4). A PCE risk of 7.5% corresponded to a risk of 2.9% in men and 3.6% in women estimated by the SCORE+HDL high-risk equation (Table 3).

The 2013 ACC/AHA guideline captured double as many men and four times more women with first MI compared with a common interpretation of the 2012 ESC guideline (SCORE ≥5% below age 60 and ≥10% above 60) (Figure 2 and 4). This contrasting performance was accentuated with the SCORE low-risk equation recommended for use in Denmark and most other non-Eastern European countries (Figure 5). PCE 7.5% corresponded to SCORE 1.5% in men and 2.0% in women (Table 3). Below age 60, only 2% of men and no women with first MI qualified for statin therapy by the ESC guideline (SCORE ≥5%), whereas 62% of men and 13% of women qualified for a class I recommendation by the ACC/AHA guideline (Figure 2). Above age 60, 12% of men and 2% of women qualified for treatment in Europe (SCORE ≥10%), in contrast to all men and 85% of women in the US.

ESC 2012 versus ESC 2003 and 2007
Predicted risk estimated by the SCORE+HDL high-risk and low-risk equations correlated perfectly (see online supplementary figure). Predicted risk was 1.7 times higher in men and 1.9 times higher in women when estimated by the high-risk equation compared with the low-risk equation. Thus, 5% risk determined by the high-risk equation recommended until 2012 corresponded to only 2.9% risk in men and 2.6% risk in women determined by the low-risk equation now recommended. Consequently, 85 of 162 males (52%) and 27 of 85 females (32%) with a first MI who would have been eligible for primary prevention with statins under the previous ESC guidelines lost their eligibility when Denmark (and many other European countries) was reclassified from a “high-risk” to a “low-risk” country in the new guidelines (Figure 2 and online supplementary figure).[1]

DISCUSSION
A “reality check” of guidelines on CVD prevention in patients with a first MI revealed that many more patients would have been eligible for primary prevention with statins by following the 2013 ACC/AHA and 2014 NICE/UK guidelines compared with the 2012 ESC guideline. The use of statins was liberalized in the US in 2013 and the UK in 2014, but indirectly restricted in many European countries in 2012 by recommending the SCORE low-risk equation instead of the high-risk equation.[1] With the low-risk equation, only 13 of 162 men (8%) and 1 of 85 women (1%) with a first MI would have qualified for primary prevention with statins, leaving ESC alone with increasingly restrictive recommendations on primary prevention with statins.

As expected, ranking patients by predicted risk estimated with different multifactorial risk equations correlated strongly, and previous studies have shown that their ability to discriminate cases from non-cases is similar for practical purposes.[18,19] Thus, the clinical performance depends critically on how accurate risk is estimated (calibration) and the decision thresholds recommended in the respective guidelines.

US guideline
With the release of the 2013 ACC/AHA guideline, a new risk calculator based on PCE was introduced.[3] We were not able to access calibration of PCE in our study population, but recent data indicates that PCE is
reasonable well calibrated (similar to SCORE) in a UK “low-risk” population.[20] This observation provides a reasonable background for comparing PCE directly with SCORE and QRISK in a European country classified as “low-risk” (Figure 3 and 5).

We estimated and compared predicted risk and found that a PCE risk of 7.5% corresponded to an ATPIII risk of ~10% in men and ~4% in women (Figure 1, Table 3), documenting that the bar for primary prevention with statin therapy deliberately was lowered by the 2013 ACC/AHA guideline, especially in women.[21,22] Concerns have been raised about the potential risk of overtreatment.[23] In patients with first MI who were 60 to 75 years of age, the sensitivity of the new class I recommendation for statin therapy (PCE ≥7.5%) was 100% in men and 85% in women (Figure 2). The new cut-point for treatment was established based on risk-benefit considerations alone,[2,3] cost-effectiveness of fixed-dose not target driven statin therapy was not questioned.[22] A recent review concluded that the new recommendations for statin therapy “generally meet societal acceptable levels of cost-effectiveness.”[24] The ACC/AHA guidelines are expected to increase the number of people eligible for primary prevention with statins in the US substantially.[25]

European guidelines

The SCORE-based ESC guidelines have always stressed that the indication for drug therapy should be based on an accurate estimate of absolute risk for fatal CVD, taking age into consideration.[1] A paradoxical consequence is that when SCORE is recalibrated to fit a lower CVD mortality, it becomes harder to get the treatment that contributed to the lower mortality. Thus, the 2012 ESC guideline indirectly restricted the use of risk-reducing statins by reclassifying many high-income European countries from “high-risk” to “low-risk” and recommending the more accurately calibrated SCORE low-risk equations instead of the high-risk equations.[1] Twenty-five European countries are now classified as “low-risk”, compared with only eight in 2007.[1] With preserved age- and risk-dependent eligibility for statin therapy, our data show that the low-risk equations capture very few people destined for a first MI (Figure 2). Obviously, the current mortality-based decision thresholds are not geared to prevent the large burden of nonfatal CVD and still increasing health care costs.

QRISK predicts an expanded CVD endpoint compared with PCE (PCE endpoints + angina and transient ischemic attack) and, consequently, risks estimated by the QRISK2-2013 risk calculator should be higher than those estimated by the PCE-based risk calculator. Nonetheless, they don't differ much (Figure 3, Table 3), which indicates that at least one of these risk models is miscalibrated in contemporary patients. However, the recent lowering of the treatment threshold from QRISK 20% to 10%[4] brings the guideline in UK close to the 2013 ACC/AHA guideline.

Contrasting recommendations after age 60

The 2013 ACC/AHA guideline recommends neither for nor against statin therapy for primary prevention in non-diabetic people above 75.[3] The 2014 NICE guideline recommends to use the same risk-based indication for primary prevention with statins up to age 85.[4] In older people, the new recommendation 55 reads as follows; “For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 48)”.[4] In contrast, the ESC guideline recommends a higher bar for statin treatment already after age 60 and provides SCORE risk charts only up to age 65.[1] Beyond age 65, the ESC guidelines provide no guidance on how to assess risk. It is possible, but not recommended, to enter age up to 100 years in the online risk calculator, HeartScore, but the age-dependent risk is capped at age 65.[17] So, in clinical practice, very few elderly people in “low-risk” countries will qualify for primary prevention with statins if the ESC guidelines are used as intended. In an elderly European population, a high eligibility for statin therapy was recently reported by calculating the risk by entering the actual age into the underlying SCORE equations and thus ignoring how SCORE is used clinically where the age-dependent risk is capped at age 65.[26]
Limitations of the traditional high-risk strategy based on prospective cohort studies

When treatment decisions are based on absolute 10-year risk for developing CVD, accurate estimation of 10-year risk is essential to treat people as intended.[27] It is problematic for several reasons. Predicting risk based on historical and potentially outdated data is risky in populations where lifestyle, medicalisation, morbidity and mortality are changing rapidly.[21,23,28,29] A contemporary (sub)population against which to update (recalibrate) a risk score is often lacking.[18,21] Applicable “natural history” cohorts are vanishing because of wider use of risk-reducing medications already at baseline and during follow-up.[21,30]

Generalisability may be questioned because of non-reproducible or inapplicable endpoints or uncertain ascertainment and adjudication.[2,10,30] Overall, a primary prevention strategy based on absolute risk is not always feasible, illustrated by the suboptimal guidance to ethnic groups other than non-Hispanic Whites and African Americans in the new ACC/AHA guidelines.[2,3]

Our study illustrates that important complementary information may be provided by a simple “really check” in contemporary patients with a first MI, revealing an extraordinarily low sensitivity of the guideline-defined threshold for intensified prevention in a European “low-risk” country.[1] Such a reality check is easy to perform world-wide, inexpensive, and provides useful information rapidly. To put it into perspective, our reality check included 247 patients hospitalized with a first MI, in the JUPITER trial only 62 nonfatal MI were observed among 8901 placebo patients during nearly 2 years of follow-up (31).

Limitations of the present study

Our study has important strengths. This analysis was performed in a representative cohort of first MI cases, with an age- and sex-distribution routinely seen in clinical practice. Thus, the actual performance of current guidelines on CVD prevention is provided. However, some potential limitations need to be addressed. A “reality check” of primary prevention guidelines requires that predictors for a first atherosclerotic event can be assessed after the event. They can with the approach used in this study. First, the strongest predictors of risk (age, sex, and smoking) can always be determined after as well as before the event, and the impact of small changes in cholesterol and blood pressure on multi-factorial risk assessment is critical only near the risk-based decision threshold. Plasma cholesterol was measured early after admission (within the first 24 hours), which today is accepted to represent baseline values;[32] plasma cholesterol was indeed only 5% lower in the 181 patients in whom a paired pre-MI value was available for comparison. The blood pressure used for estimation of predicted risk was obtained in a stable phase, either before MI (previous hospitalization or general practitioner) or after recovery from the acute phase (just before hospital discharge or first visit to the rehabilitation clinic). The mean systolic blood pressure (± SD) measured before MI was 139.4 (±20.3) mmHg (n=103), after MI 137.1 (±19.0) mmHg (n=293, p=0.28). Only few non-diabetic, CVD-free patients used statin before the first MI (n=26, age 40-75), and they were excluded. In patients with a first MI, only the detection rate (sensitivity) of decision thresholds can be determined, not the specificity and risk of overtreatment. However, if a decision threshold captures only a minority of those it was intended to identify, its utility may be questioned. Given that the 2013 ACC/AHA and the 2014 NICE/UK guidelines lowered the threshold for primary prevention with statins based on careful risk-benefit and cost-effectiveness considerations,[3,4,33] the appropriateness of the much lower sensitivity of the SCORE-based treatment threshold recommended for use in many high-income European countries[1] deserves to be reconsidered.

Conclusion

The 2012 ESC and the 2013 ACC/AHA and 2014 NICE/UK guidelines differ substantially in their ability to secure statin therapy to those destined for a first MI. In Europe, with the exception of UK, eligibility for primary prevention with statins is becoming increasingly restricted in non-Eastern European countries by updating only the mortality-based SCORE equations, not the risk thresholds on which treatment decisions are based. In the US and UK, a treatment threshold based on risk-benefit and cost-effectiveness considerations[3,4,24,33] has now been defined, leading to a wider eligibility for primary prevention with statin therapy.
Acknowledgements
We thank Ole May, Ole Gotzsche, Helle Kanstrup, Jette Bertelsen, Helle K. Jensen, Willemijn Comuth and Kim Sivesgaard for their assistance in collecting information on traditional risk factors from the medical records.

Contributors
MB and FE contributed equally to this study, including study design, data analysis, interpretation of the results, drafting the manuscript, and final approval of the manuscript. Both authors take full responsibility for the work.

Funding
This work was supported by the Institute of Clinical Medicine at Aarhus University, Denmark.

Competing interests
None

Ethics approval
The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.

Data sharing statement
No additional data are available.

FIGURE LEGENDS

Figure 1. Eligibility for statin therapy by ACC/AHA versus ATP III.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the Adult Treatment Panel III (ATP III) risk calculator correlated strongly (Spearman’s rho 0.86 in men and 0.82 in women; p<0.0001). Compared with ATP III risk ≥10%, PCE risk ≥7.5% captured nearly the same men but substantially more women with first MI. The ATP III risk calculator only provides whole numbers, and the absolute risk is capped at 30%.
For PCE <7.5%, y = 1.261*x + 0.00026 in men, and y = 0.4476*x + 0.7274 in women.

Figure 2. Proportion (%) of patients with first myocardial infarction who would have been eligible for primary prevention with statins.
The SCORE Low-Risk equation is recommended for use in Denmark and 24 other European countries with a relatively low cardiovascular mortality. The exact values and guideline-defined decision thresholds behind this bar diagram are shown in the online appendix (see supplementary table).

Figure 3. Eligibility for statin therapy by ACC/AHA versus NICE/UK.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the QRISK2-2013 risk equation correlated strongly (Spearman’s rho 0.94 in men and 0.97 in women; p<0.0001). Compared with PCE risk ≥7.5%, QRISK ≥20% (indication for statin therapy in the previous NICE guideline) identified much fewer patients with first MI, whereas QRISK ≥10% (indication for statins in the 2014 NICE update) identified nearly the same patients, especially among women.
For PCE <7.5%, y = 0.6385*x + 2.171 in men, and y = 1.308*x + 0.2708 in women.

Figure 4. Eligibility for statin therapy by ACC/AHA versus ESC “high-risk” countries.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the SCORE+HDL High-Risk equation correlated strongly (Spearman’s rho 0.89 in men and 0.84 in women; p<0.0001). The PCE-defined treatment threshold of 7.5% captured double as many men and four times more women with first MI compared with the SCORE-defined treatment thresholds of 5% below age 60 and 10% above 60.
For PCE <7.5%, y = 0.3514*x + 0.3034 in men, and y = 0.6065*x + 0.9550 in women.

Figure 5. Eligibility for statin therapy by ACC/AHA versus ESC “low-risk” countries.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and SCORE+HDL Low-Risk equation correlated strongly (Spearman’s rho 0.91 in men and 0.83 in women; p<0.0001). Only 13 of 162 men (8%) and 1 of 85 women (1%) with first MI qualified for primary prevention with statins using the SCORE-defined treatment threshold of 5% below age 60 and 10% above 60.
For PCE <7.5%, y=0.1519*x+0.3258 in men, and y=0.3203*x-0.4519 in women.
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33. Hawkes N. NICE sticks to its advice to drop threshold for prescribing statins. BMJ. 2014 Jul 17;349:g4694. doi: 10.1136/bmj.g4694.
Reality check of high-risk strategies for primary prevention of cardiovascular disease in Europe and United States

Real-life evaluation of European and American high-risk strategies for primary prevention of cardiovascular disease in patients with first myocardial infarction

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ABSTRACT

Objective
To determine the detection rate (sensitivity) of the high-risk strategy recommended in the European (ESC and NICE/UK) and American (ACC/AHA) guidelines on cardiovascular disease (CVD) prevention. In particular, to evaluate the ability to ensure statin therapy to contemporary Europeans destined for a first myocardial infarction (MI), cardiovascular event.

Design
393 consecutive statin-naive, non-diabetic, CVD-free patients hospitalized for a first MI, 247 of whom were 40 to 75 years of age. We assumed they had undergone a health check the day before their MI and estimated the predicted risk.

Primary outcome
Sensitivity of the risk-based eligibility for primary prevention with statin therapy recommended by the guidelines.

Results
All recommended risk scores rank-ordered patients similarly, but the sensitivity of the cut-point above which statin therapy should be considered differed substantially. In younger patients (age 40-60), 62% of men and 13% of women qualified for statin therapy by ACC/AHA criteria, compared with only 2% of men and no women using the ESC criteria recommended for most non-Eastern European countries. In those 60 to 75 years of age, the ACC/AHA guidelines captured all men and 85% of women, compared with 12% and 2%, respectively, using the new ESC guideline. This guideline restricted the eligibility for primary prevention with statins substantially by reclassifying many European countries from “high-risk” to “low-risk”, whereas the eligibility was expanded in the ACC/AHA guideline and proposed and the new NICE/UK update guidelines by lowering the decision threshold.

Conclusions
The 2012 ESC guidelines differ substantially from the 2013 ACC/AHA and proposed 2014 NICE/UK guidelines in ability to secure statin therapy to those destined for a first MI. A great opportunity for primary prevention with statins remains unexploited in Europe.

Keywords: Prevention - Cardiovascular disease - Risk assessment - SCORE - Statin
Strengths and limitations of this study

- Cohort of consecutive, contemporary patients hospitalized with a first MI, representing those seen in clinical practice today.
- Estimation of the detection rate (sensitivity) of a high-risk strategy to prevent CV DMI in a representative cohort of contemporary non-diabetic patients with failed prevention (first MI).
- A “reality check” of a high-risk strategy in contemporary patients with failed prevention is easy to perform world-wide, inexpensive, and provides useful information rapidly.
- Only the detection rate (sensitivity), not the specificity, can be determined by focusing only on those who develop CVD. However, the specificity can be deduced from already-existing knowledge.
INTRODUCTION
The guidelines on cardiovascular disease (CVD) prevention were revised recently in both Europe and the United States. [1-4] In 2012, the European Society of Cardiology (ESC) continued to stress the importance of using a well-calibrated version of the mortality-based SCORE (Systematic Coronary Risk Evaluation) algorithm in the primary prevention of CVD. Consequently, because of secular trends of declining CVD mortality, many European countries were reclassified from “high-risk” to “low-risk” and recommended to use the SCORE low-risk algorithm instead of the high-risk algorithm. The age-dependent risk thresholds above which primary prevention with statin therapy should be considered were preserved. In 2013, the American College of Cardiology and the American Heart Association (ACC/AHA) released new guidelines [2,3] in which a risk calculator based on new risk equations (Pooled Cohort Equations, PCE) was introduced, together with new risk-dependent thresholds above which primary prevention with statin therapy should be considered. More recently (February 2014) in 2014, the National Institute for Health and Care Excellence (NICE) in the UK proposed to lower the recommended threshold for primary prevention with statin therapy based on QRISK (scheduled for publication July 2014). [4] endorsed by the third Joint British Societies’ (JBS3) consensus recommendations for the prevention of CVD.[5] Thus, in current and draft European and American guidelines, different criteria are used to identify people in need for primary prevention with statins.

These guidelines are endorsing the paradigm of matching the intensity of risk-reducing therapy to the absolute short-term (10-year) risk of the patient. [1-4] Although it takes many years of follow-up to evaluate the accuracy (calibration) of how accurate the recommended risk equations (SCORE, PCE, and QRISK) are calibrated, their ability to rank-order people by predicted risk and ensuring statin therapy to those at highest risk can be evaluated and compared in contemporary patients with a first CVD event. We did such a “reality check” of the new guidelines and those they replaced in patients hospitalized for a first myocardial infarction (MI).

METHODS
Study population
We reviewed the medical records of 605 consecutive patients admitted to three hospitals in Denmark (departments of cardiology/medicine at Aarhus University Hospital and the Regional Hospitals in Herning and Randers) with a first acute MI between January 1 through December 31, 2011. The universal definition of MI is implemented in Denmark, [6] and the patients were identified via hospital registers using ICD-10 codes I21.0 through I21.9. Patients with preexisting CVD (n=48), diabetes (n=92), incomplete risk factor information (n=32), and statin users (n=40) were excluded (diabetic patients do not belong to the target population for risk assessment defined by the ESC and ATP III guidelines), leaving 393 statin-naïve, non-diabetic, CVD-free patients with first MI. To match the age range used in the ACC/AHA guideline, we limited the study population to those 40 to 75 years of age (n=247; 162 men and 85 women). We extracted information on traditional risk factors (age, sex, smoking status, total cholesterol, high-density lipoprotein (HDL) cholesterol, and systolic blood pressure) as previously described. [6,7] Plasma cholesterol was measured early after admission (within the first 24 hours), and available pre-MI values were used to assess possible changes related to the acute phase of MI. The blood pressure used for estimation of risk was measured in a stable phase, either before MI (previous hospitalization or general practitioner) or after recovery from the acute phase (just before hospital discharge or first visit to the rehabilitation clinic).

Estimation of predicted risk and eligibility for statin
The guideline-recommended risk equations and web calculators used to determine predicted risk, risk factors (predictors), clinical endpoints, definitions of high-risk and recommended decision thresholds above which statin therapy should be considered are shown in Table 1 and described in the online appendix.
Table 1. Guidelines and risk equations used to estimate 10-year risk for a first cardiovascular event (primary prevention)

<table>
<thead>
<tr>
<th>Guideline Risk equation</th>
<th>Derivation cohorts</th>
<th>Eligibility for statin therapy</th>
<th>Predicted outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2012 ESC[1]</strong></td>
<td>Europe[10] 1967-1986</td>
<td>≥5% (age ≤60) ≥10% (age 60-65)</td>
<td>Fatal ASCVD: CHD, stroke etc</td>
</tr>
<tr>
<td><strong>Pooled Cohort Equations (PCE)</strong></td>
<td>FHS: 30-59 CARDIA: 18-30 ARIC: 35-74 CHS: ≥65</td>
<td>≥7.5% (weak/class IIa)</td>
<td>ASCVD: nonfatal MI, fatal CHD, fatal and nonfatal stroke</td>
</tr>
<tr>
<td><strong>NCEP-ATP III[7,8]</strong></td>
<td>Framingham 1971[8]</td>
<td>20% (unconditional) 10% (conditional)</td>
<td>Hard CHD: nonfatal MI, fatal CHD</td>
</tr>
</tbody>
</table>

SCORE = Systematic CORonary Risk Evaluation; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; NCEP-ATP III = National Cholesterol Education Program – Adult Treatment Panel III; MI = myocardial infarction; NICE = National Institute for Health and Care Excellence; TIA = Transient Ischemic Attack; CHS = Cardiovascular Health Study; FHS = Framingham Heart Study; CARDIA = Coronary Artery Risk Development in Young Adults Study; ARIC = Atherosclerosis Risk In Communities study; *Year baseline examination started; #Ten-year risk for the predicted outcomes;

Comparison of CVD prevention guidelines
We evaluated and compared the performance of the American and European primary prevention guidelines shown in Table 1. For each patient we calculated the absolute 10-year risk for the predicted outcomes using the recommended risk equations or calculators. In accordance with the SCORE risk charts [1] and the online risk calculator HeartScore,[17] the age-dependent risk was capped at age 65 when estimating risk using the SCORE algorithms. The guidelines were compared in three steps as described in the online appendix.

Ethical considerations
The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.
RESULTS
Baseline characteristics of the study population are shown in Table 2. We identified 393 statin-naïve, non-diabetic, CVD-free patients with first MI of whom 13 below age 40 and 133 above age 75 were excluded, leaving 247 patients (162 men, 85 women) for the present study.

Table 2. Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (40-75 years)</th>
<th>40-60 years</th>
<th>61-75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients no.</td>
<td>247</td>
<td>96 (39%)</td>
<td>151 (61%)</td>
</tr>
<tr>
<td>Age</td>
<td>61.9 (9.3)</td>
<td>51.7 (4.9)</td>
<td>68.4 (4.2)</td>
</tr>
<tr>
<td>Men</td>
<td>162 (66%)</td>
<td>65 (68%)</td>
<td>97 (64%)</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>137 (19.8)</td>
<td>131 (19.0)</td>
<td>140 (21.4)</td>
</tr>
<tr>
<td>Plasma parameters, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.3 (1.0)</td>
<td>5.4 (1.0)</td>
<td>5.2 (1.0)</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>3.3 (0.9)</td>
<td>3.4 (0.9)</td>
<td>3.3 (0.9)</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.3 (0.4)</td>
<td>1.2 (0.4)</td>
<td>1.3 (0.4)</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>53</td>
<td>63</td>
<td>38</td>
</tr>
<tr>
<td>Blood pressure lowering therapy, %</td>
<td>30</td>
<td>21</td>
<td>35</td>
</tr>
</tbody>
</table>

| Continuous variables: mean (SD)        | LDL = low-density lipoprotein; HDL = high-density lipoprotein; |

2013 ACC/AHA versus ATP III
Ranking patients with first MI by predicted risk estimated by PCE (used in the new ACC/AHA risk calculator) and the previously recommended ATP III risk calculator correlated strongly (Figure 1). PCE risk ≥7.5%, which is a strong/class I recommendation for statin therapy, corresponded to ATP III risk ≥9.5% in men and ≥4.1% in women and, compared with ATP III risk ≥10%, captured nearly the same men but substantially more women with first MI (Figure 1 and 2, Table 3).

Table 3. Risk equivalent to PCE 7.5% and 5% determined by other risk equations*

<table>
<thead>
<tr>
<th>Predicted 10-year risk of diverse CVD outcomes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCE 2013</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*Based on linear regression of those with PCE risk <7.5% (Figure 1 and 3-5).
ATP III = Adult Treatment Panel III; CVD = cardiovascular disease; HDL = high-density lipoprotein; PCE = Pooled Cohort Equations; SCORE = Systematic COronary Risk Evaluation;
2013 ACC/AHA versus 2010 and draft 2014 NICE/UK

Ranking patients with first MI by predicted risk estimated by PCE and the QRISK risk calculator correlated strongly (Figure 3). A PCE risk of 7.5% corresponded to a risk of 7.0% in men and 10.1% in women estimated by QRISK (Table 3). Thus, with the 2014 NICE/UK recommendation to lower the QRISK-based threshold for statin therapy from 20% to 10%, the eligibility for primary prevention with statins is nearly similar in the US and the UK (Figure 2 and 3).

Compared with the ACC/AHA guidelines, much fewer patients with first MI qualified for primary prevention with statins using the 2010 NICE/UK guidelines (Figure 2). Below age 60, only 2% of men and no women qualified for treatment by the UK guideline (QRISK ≥20%), whereas 62% of men and 13% of women qualified by the ACC/AHA guideline (PCE ≥7.5%). However, the eligibility for statin was nearly similar with UK and US guidelines if the treatment threshold was lowered from QRISK 20% to 10% as recently proposed by the 2014 draft update of NICE/UK guidelines (Figure 2 and 3).[4]

2013 ACC/AHA versus 2012 ESC

Ranking patients with first MI by predicted risk estimated by PCE and SCORE+HDL high-risk equations correlated strongly (Figure 4). A PCE risk of 7.5% corresponded to a risk of 2.9% in men and 3.6% in women estimated by the SCORE+HDL high-risk equation (Table 3).

The 2013 ACC/AHA guideline captured double as many men and four times more women with first MI compared with a common interpretation of the 2012 ESC guideline (SCORE ≥5% below age 60 and ≥10% above 60) (Figure 2 and 4). This contrasting performance was accentuated with the SCORE low-risk equation recommended for use in Denmark and most other non-Eastern European countries (Figure 5). PCE 7.5% corresponded to SCORE 1.5% in men and 2.0% in women (Table 3). Below age 60, only 2% of men and no women with first MI qualified for statin therapy by the ESC guideline (SCORE ≥5%), whereas 62% of men and 13% of women qualified for a class I recommendation by the ACC/AHA guideline (Figure 2). Above age 60, 12% of men and 2% of women qualified for treatment in Europe (SCORE ≥10%), in contrast to all men and 85% of women in the US.

ESC 2012 versus ESC 2003 and 2007

Predicted risk estimated by the SCORE+HDL high-risk and low-risk equations correlated perfectly (see online supplementary figure). Predicted risk was 1.7 times higher in men and 1.9 times higher in women when estimated by the high-risk equation compared with the low-risk equation. Thus, 5% risk determined by the high-risk equation recommended until 2012 corresponded to only 2.9% risk in men and 2.6% risk in women determined by the low-risk equation now recommended. Consequently, 85 of 162 males (52%) and 27 of 85 females (32%) with a first MI who would have been eligible for primary prevention with statins under the previous ESC guidelines lost their eligibility when Denmark (and many other European countries) was reclassified from a “high-risk” to a “low-risk” country in the new guidelines (Figure 2 and online supplementary figure).[1]

DISCUSSION

A “reality check” of guidelines on CVD prevention in patients with a first MI revealed that many more patients would have been eligible for primary prevention with statins by following the 2013 ACC/AHA and 2014 NICE/UK guidelines compared with the 2012 ESC and 2010 NICE guidelines. The use of statins was liberalized in the US in 2013 and the UK in 2014, but indirectly restricted in many European countries in 2012 by recommending the SCORE low-risk equation instead of the high-risk equation.[1] With the low-risk equation, only 13 of 162 men (8%) and 1 of 85 women (1%) with a first MI would have qualified for primary prevention with statins. Lowering the treatment threshold as recommended by the 2014 draft update of the NICE/UK guideline[4] will leave ESC alone with increasingly restrictive recommendations on primary prevention with statins.
As expected, ranking patients by predicted risk estimated with different multifactorial risk equations correlated strongly, indicating and previous studies have shown that their ability to discriminate cases from non-cases is similar for practical purposes. Thus, the clinical performance depends critically on how accurate risk is estimated (calibration) and the decision thresholds recommended in the respective guidelines.

**US guideline**

With the release of the 2013 ACC/AHA guideline, a new risk calculator based on PCE was introduced. We were not able to access calibration of PCE in our study population, but recent data indicates that PCE is reasonable well calibrated (similar to SCORE) in a UK “low-risk” population. This observation provides a reasonable background for comparing PCE directly with SCORE and QRISK in a European country classified as “low-risk” (Figure 3 and 5).

We estimated and compared predicted risk and found that a PCE risk of 7.5% corresponded to an ATP III risk of ~10% in men and ~4% in women (Figure 1, Table 3), documenting that the bar for primary prevention with statin therapy deliberately was lowered by the 2013 ACC/AHA guideline, especially in women. Concerns have been raised about the potential risk of overtreatment. In patients with first MI who were 60 to 75 years of age, the sensitivity of the new class I recommendation for statin therapy (PCE ≥7.5%) was 100% in men and 85% in women (Figure 2). The new cut-point for treatment was established based on risk-benefit considerations alone, cost-effectiveness of fixed-dose not target driven statin therapy was not questioned. A recent review concluded that the new recommendations for statin therapy “generally meet societal acceptable levels of cost-effectiveness.” The ACC/AHA guidelines are expected to increase the number of people eligible for primary prevention with statins in the US substantially.

Immediately after release of the 2013 ACC/AHA guideline, the new PCE-based risk model was accused of being miscalibrated because it systematically overestimated risk in certain external validation cohorts, which could lead to massive overtreatment with statin. A possible overestimation of risk in contemporary populations was realized in the guideline document and alternative explanations for the unexpected results obtained in the validation cohorts were provided. In our patients with a first MI, ≥7.5% risk estimated by the new risk equation captured the same proportion of patients as ≥9.5% risk in men and ≥4.1% in women estimated by the prior ATP III risk equation. Because the clinical outcomes predicted by PCE are more numerous than those predicted with ATP III by including stroke in addition to hard CHD, PCE in fact underestimated risk in men compared with ATP III. Because ischemic stroke is nearly as common as MI in women, PCE risk ≥7.5% seems commensurate with ATP III risk ≥4.1%. Thus, compared with the risk model it replaced, the new PCE-based risk model does not seem to overestimate risk at or below the new risk thresholds for statin therapy. Recently, PCE was found to be well-calibrated in a contemporary US cohort and PCE performed reasonably well (not inferior to SCORE) in a UK “low-risk” population.

If the new guidelines give rise to wider use of statin for primary prevention of CVD, a plausible explanation is that the bar for treatment deliberately was lowered substantially by these guidelines. The cut-point for treatment was established based on risk-benefit considerations alone, cost-effectiveness of fixed-dose not target driven statin therapy was not questioned. The new ACC/AHA guidelines are expected to increase the number of people eligible for primary prevention with statin in the US substantially.

**European guidelines**

The SCORE-based ESC guidelines have always stressed that the indication for drug therapy should be based on an accurate estimate of absolute risk for fatal CVD, taking age into consideration. A paradoxical consequence is that when SCORE is recalibrated to fit a lower CVD mortality, it becomes harder to get the treatment that contributed to the lower mortality. Thus, the 2012 ESC guideline indirectly restricted the use of risk-reducing statins by reclassifying many high-income European countries from “high-risk” to “low-risk” and recommending the more accurately calibrated SCORE low-risk equations instead of the high-risk equations. Twenty-five European countries are now classified as “low-risk”, compared with only eight in 2007. With preserved age- and risk-dependent eligibility for statin therapy, our data show that the low-risk equations capture very few people destined for a first MI (Figure 2). Obviously, the current mortality-based
decision thresholds are not geared to prevent the large burden of nonfatal CVD and still increasing health care costs.

QRISK predicts an expanded CVD endpoint compared with PCE (PCE endpoints + angina and transient ischemic attack) and, consequently, risks estimated by the QRISK2-2013 risk calculator should be higher than those estimated by the PCE-based risk calculator. Nonetheless, they don't differ much (Figure 3, Table 3), which indicates that at least one of these risk models is miscalibrated in contemporary patients. Today, substantially more people would qualify for primary prevention with statin based on PCE >7.5% (recommended in US) compared to QRISK >20% (recommended in UK) (Figure 2). However, the recent lowering of the treatment threshold from QRISK 20% to 10%, as proposed by NICE in the February 2014 draft update,[4] will bring the guideline in UK close to the 2013 ACC/AHA guideline.

Contrasting recommendations after age 60
The 2013 ACC/AHA guideline recommends neither for nor against statin therapy for primary prevention in non-diabetic people above 75.[3] The NICE guideline recommends that people aged 75 or older should be considered for statin treatment, particularly those who smoke or have high blood pressure.[9] The 2014 NICE guideline recommends to use the same risk-based indication for primary prevention with statins up to age 85.[4] In older people, the new recommendation 55 reads as follows; “For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 48)” Consider atorvastatin 20 mg for people older than 85 years because they are likely to benefit from statin treatment.[4]

In contrast, the ESC guideline recommends a higher bar for statin treatment already after age 60 and provides SCORE risk charts only up to age 65.[1] Beyond age 65, the ESC guidelines provide no guidance on how to assess risk. It is possible, but not recommended, to enter age up to 100 years in the online risk calculator, HeartScore, but the age-dependent risk is capped at age 65.[17] So, in clinical practice, very few elderly people in “low-risk” countries will qualify for primary prevention with statins if the ESC guidelines are used as intended. In an elderly European population, a high eligibility for statin therapy was recently reported by calculating the risk by entering the actual age into the underlying SCORE equations and thus ignoring how SCORE is used clinically where the age-dependent risk is capped at age 65.[268]

The future: reality check in contemporary patients with a first CVD event
Limitations of the traditional high-risk strategy based on prospective cohort studies
When treatment decisions are based on absolute 10-year risk for developing CVD, accurate estimation of 10-year risk is essential to treat people as intended.[27] It is problematic for several reasons. Predicting risk based on historical and potentially outdated data is risky in populations where lifestyle, medicalisation, morbidity and mortality are changing rapidly.[21,23,28,29,2020-22,29] A contemporary (sub)population against which to update (recalibrate) a risk score is often lacking.[18,2122] Applicable “natural history” cohorts are vanishing because of wider use of risk-reducing medications already at baseline and during follow-up.[21,3022,24] Generalisability may be questioned because of non-reproducible or inapplicable endpoints or uncertain ascertainment and adjudication.[2,10,3024] Overall, a primary prevention strategy based on absolute risk is not always feasible, illustrated by the suboptimal guidance to ethnic groups other than non-Hispanic Whites and African Americans in the new ACC/AHA guidelines.[2,3]

Our study illustrates that important complementary information may be provided by a simple “really check” in contemporary patients with a first MI, revealing an extraordinarily low sensitivity of the guideline-defined threshold for intensified prevention in a European “low-risk” country.[1] Such a reality check is easy to perform world-wide, inexpensive, and provides useful information rapidly. To put it into perspective, our reality check included 247 patients hospitalized with a first MI, in the JUPITER trial only 62 nonfatal MI were observed among 8901 placebo patients during nearly 2 years of follow-up (31). Alternatively and/or complementary, a reality check in contemporary patients with a first MI can reveal how a high-risk strategy performs in clinical practice. First, the sensitivity of the decision thresholds can be assessed. Second, because the discriminative performance of traditional risk scores vary little across populations,[18,19] an estimate of the corresponding specificity can be deduced from a representative...
receiver operating characteristic curve. Third, the proportion of first MI prevented by statin therapy can be estimated. In the present study, 40 (9%) of 433 CVD-free, non-diabetic patients used statin before their first MI. Assuming statin therapy reduces the risk by 30%, without statin we would have expected only 17 more first AMI cases (40/0.7 = 57), indicating that the current use of statin in this population prevented very few first AMIs (~4%). Finally, a reality check is easy to perform world-wide, inexpensive, and provides useful information rapidly.

Limitations of the present study
Our study has important strengths. This analysis was performed in a representative cohort of first MI cases, with an age- and sex-distribution routinely seen in clinical practice. Thus, the actual performance of current guidelines on CVD prevention is provided. However, some potential limitations need to be addressed. A "reality check" of primary prevention guidelines requires that predictors for a first atherosclerotic event can be assessed after the event. They can with the approach used in this study. First, the strongest predictors of risk (age, sex, and smoking) can always be determined after as well as before the event, and the impact of small changes in cholesterol and blood pressure on multi-factorial risk assessment is critical only near the risk-based decision threshold. Plasma cholesterol was measured early after admission (within the first 24 hours), which today is accepted to represent baseline values;[40,32] plasma cholesterol was indeed only 5% lower in the 181 patients in whom a paired pre-MI value was available for comparison. The blood pressure used for estimation of predicted risk was obtained in a stable phase, either before MI (previous hospitalization or general practitioner) or after recovery from the acute phase (just before hospital discharge or first visit to the rehabilitation clinic). The blood pressure was similar before and after MI in 99 patients in whom paired values were available for comparison.[6] The mean systolic blood pressure (±SD) measured before MI was 139.4 (±20.3) mmHg (n=103), after MI 137.1 (±19.0) mmHg (n=293, p=0.28). Only few non-diabetic, CVD-free patients used statin before the first MI (n=26, age 40-75 years, 9%), and they were excluded. In patients with a first MI, only the detection rate (sensitivity) of decision thresholds can be determined, not the specificity. However, if a decision threshold captures only a minority of those it was intended to identify, the appropriateness of the recommended strategy needs to be reconsidered. In patients with a first MI, only the detection rate (sensitivity) of decision thresholds can be determined, not the specificity and risk of overtreatment. However, if a decision threshold captures only a minority of those it was intended to identify, its utility may be questioned. Given that the 2013 ACC/AHA and the 2014 NICE/UK guidelines lowered the threshold for primary prevention with statins based on careful risk-benefit and cost-effectiveness considerations,[3,4,33] the appropriateness of the much lower sensitivity of the SCORE-based treatment threshold recommended for use in many high-income European countries[1] deserves to be reconsidered.

Conclusion
The 2012 ESC and the 2013 ACC/AHA and 2014 NICE/UK guidelines differ substantially in their ability to secure statin therapy to those destined for a first MI. In Europe, with the exception of UK, eligibility for primary prevention with statins is becoming increasingly restricted in non-Eastern European countries by updating only the mortality-based SCORE equations, not the risk thresholds on which treatment decisions are based. In the US and possibly UK, a treatment threshold based on risk-benefit[3] and cost-effectiveness[4] considerations[3,4,24,33] has now been defined, leading to a wider eligibility for primary prevention with statin therapy.

Acknowledgements
We thank Ole May, Ole Gotzsche, Helle Kanstrup, Jette Bertelsen, Helle K. Jensen, Willemijn Comuth and Kim Sivesgaard for their assistance in collecting information on traditional risk factors from the medical records.

Contributors
Both authors contributed equally to this study, including study design, data analysis, interpretation of the results, drafting the manuscript, and final approval of the manuscript. Both authors take full responsibility for the work.
Funding
This work was supported by the Institute of Clinical Medicine at Aarhus University, Denmark.

Competing interests
None

Ethics approval
The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.

Data sharing statement
No additional data are available.
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FIGURE LEGENDS

Figure 1. Eligibility for statin therapy by ACC/AHA versus ATP III.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the Adult Treatment Panel III (ATP III) risk calculator correlated strongly (Spearman’s rho 0.86 in men and 0.82 in women; p<0.0001). Compared with ATP III risk ≥10%, PCE risk ≥7.5% captured nearly the same men but substantially more women with first MI. The ATP III risk calculator only provides whole numbers, and the absolute risk is capped at 30%. For PCE <7.5%, y = 1.261*x + 0.00026 in men, and y = 0.4476*x + 0.7274 in women.

Figure 2. Proportion (%) of patients with first myocardial infarction who would have been eligible for primary prevention with statins.
The SCORE Low-Risk equation is recommended for use in Denmark and 24 other European countries with a relatively low cardiovascular mortality. The exact values and guideline-defined decision thresholds behind this bar diagram are shown in the online appendix (see supplementary table).

Figure 3. Eligibility for statin therapy by ACC/AHA versus NICE/UK.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the QRISK2-2013 risk equation correlated strongly (Spearman’s rho 0.94 in men and 0.97 in women; p<0.0001). Compared with PCE risk ≥7.5%, QRISK ≥20% (indication for statin therapy in the previous NICE guideline 2010 NICE/UK) identified much fewer patients with first MI, whereas QRISK ≥10% (indication for statins in draft the 2014 NICE update) identified nearly the same patients, especially among women. For PCE <7.5%, y = 0.6385*x + 2.171 in men, and y = 1.308*x + 0.2708 in women.

Figure 4. Eligibility for statin therapy by ACC/AHA versus ESC “high-risk” countries.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the SCORE+HDL High-Risk equation correlated strongly (Spearman’s rho 0.89 in men and 0.84 in women; p<0.0001). The PCE-defined treatment threshold of 7.5% captured double as many men and four times more women with first MI compared with the SCORE-defined treatment thresholds of 5% below age 60 and 10% above 60. For PCE <7.5%, y = 0.3514*x + 0.3034 in men, and y = 0.6065*x + 0.9550 in women.

Figure 5. Eligibility for statin therapy by ACC/AHA versus ESC “low-risk” countries.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and SCORE+HDL Low-Risk equation correlated strongly (Spearman’s rho 0.91 in men and 0.83 in women; p<0.0001). Only 13 of 162 men (8%) and 1 of 85 women (1%) with first MI qualified for primary prevention with statins using the SCORE-defined treatment threshold of 5% below age 60 and 10% above 60. For PCE <7.5%, y=0.1519*x+0.3258 in men, and y=0.3203*x-0.4519 in women.
Figure 1. Eligibility for statin therapy by ACC/AHA versus ATP III.

Predicted risk estimated by the Pooled Cohort Equations (PCE) and the Adult Treatment Panel III (ATP III) risk calculator correlated strongly (Spearman’s rho 0.86 in men and 0.82 in women; p<0.0001). Compared with ATP III risk ≥10%, PCE risk ≥7.5% captured nearly the same men but substantially more women with first MI. The ATP III risk calculator only provides whole numbers, and the absolute risk is capped at 30%.

For PCE <7.5%, y = 1.261*x + 0.00026 in men, and y = 0.4476*x + 0.7274 in women.
Figure 2. Proportion (%) of patients with first myocardial infarction who would have been eligible for primary prevention with statin.

The SCORE Low-Risk equation is recommended for use in Denmark and 24 other European countries with a relatively low cardiovascular mortality. The exact values and guideline-defined decision thresholds behind this bar diagram are shown in the online appendix (see supplementary table).

254x190mm (96 x 96 DPI)
Figure 3. Eligibility for statin therapy by ACC/AHA versus NICE/UK.
Predicted risk estimated by the Pooled Cohort Equations (PCE) and the QRISK2-2013 risk equation correlated strongly (Spearman’s rho 0.94 in men and 0.97 in women; p<0.0001). Compared with PCE risk ≥7.5%, QRISK ≥20% (indication for statin therapy in the previous NICE guideline) identified much fewer patients with first MI, whereas QRISK ≥10% (indication for statins in the 2014 NICE update) identified nearly the same patients, especially among women.

For PCE <7.5%, \( y = 0.6385x + 2.171 \) in men, and \( y = 1.308x + 0.2708 \) in women.

125x56mm (300 x 300 DPI)
Figure 4. Eligibility for statin therapy by ACC/AHA versus ESC “high-risk” countries.

Predicted risk estimated by the Pooled Cohort Equations (PCE) and the SCORE+HDL High-Risk equation correlated strongly (Spearman’s rho 0.89 in men and 0.84 in women; p<0.0001). The PCE-defined treatment threshold of 7.5% captured double as many men and four times more women with first MI compared with the SCORE-defined treatment thresholds of 5% below age 60 and 10% above 60.

For PCE <7.5%, $y = 0.3514x + 0.3034$ in men, and $y = 0.6065x + 0.9550$ in women.

275x131mm (300 x 300 DPI)
Figure 5. Eligibility for statin therapy by ACC/AHA versus ESC “low-risk” countries.

Predicted risk estimated by the Pooled Cohort Equations (PCE) and SCORE+HDL Low-Risk equation correlated strongly (Spearman’s rho 0.91 in men and 0.83 in women; p<0.0001). Only 13 of 162 men (8%) and 1 of 85 women (1%) with first MI qualified for primary prevention with statin using the SCORE-defined treatment threshold of 5% below age 60 and 10% above 60.

For PCE <7.5%, y=0.1519*x+0.3258 in men, and y=0.3203*x-0.4519 in women.

277x126mm (300 x 300 DPI)
Online Appendix

Real-life evaluation of European and American high-risk strategies for primary prevention of cardiovascular disease in patients with first myocardial infarction

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Supplementary Material

- Supplementary Methods
- Supplementary Table
- Supplementary Figure
Supplementary Methods

Estimation of predicted risk and eligibility for statins

The guideline-recommended risk equations and web calculators used to determine predicted risk, risk factors (predictors), clinical endpoints, definitions of high-risk and recommended decision thresholds above which statin therapy should be considered are shown in Table 1 in the printed article and described below.

The 2012 ESC recommendations for primary prevention are based on the SCORE model introduced in 2003 that predicts 10-year risk for fatal CVD in people 40 to 65 years of age.[1] Two standard SCORE risk charts/equations are available, one for countries with a high incidence of fatal CVD, the other for countries with a low incidence. Denmark, together with many other European countries, was reclassified from “high-risk” to “low-risk” in 2012 and recommended to use the SCORE low-risk equation instead of the high-risk equation. As another novelty, HDL-adjusted risk estimates became available in 2012, either as risk charts or the electronic version of SCORE, HeartScore.[2] HeartScore allows entry of age up to 100 years but the age-dependent risk is capped at age 65. The LDL-C dependent eligibility for statin therapy is based on both estimated 10-year risk and age, expressed in the following way: “In general, those with a risk of CVD death of ≥5% qualify for intensive advice, and may benefit from drug treatment. At risk levels >10%, drug treatment is more frequently required. In persons older than 60, these thresholds should be interpreted more leniently, because their age-specific risk is normally around these levels, even when other cardiovascular risk factor levels are ‘normal’.”[1] While no universally applicable risk threshold for statin therapy is given, a common interpretation is that statin therapy should be considered at SCORE ≥5% (defined as high risk) below age 60 and ≥10% (defined as very high risk) above 60.

The 2013 ACC/AHA recommendations for primary prevention are based on the newly developed PCE that predict 10-year risk for atherosclerotic CVD (ASCVD) defined as nonfatal MI, CHD death, and fatal and nonfatal stroke.[3,4] The downloadable PCE-based risk calculator provides race- and sex-specific 10-year and lifetime risks of ASCVD in nonhispanic Whites and nonHispanic African Americans.[5] For other ethnic groups, use of the sex-specific estimates calculated for nonhispanic Whites may be considered (expert opinion/IIB recommendation).[4] In adults 40 to 75 years of age, eligibility for statin therapy is PCE ≥7.5% (strong/class I recommendation) and 5% to <7.5% (weak/class IIa recommendation).[4]

The 2013 ACC/AHA guideline replaced the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program.[6,7] ATP III-based risk assessment used a Framingham-derived risk equation that predicted 10-year risk for hard coronary heart disease (CHD) defined as nonfatal MI and fatal CHD. The web-based risk calculator is still available.[8] The treatment algorithm for primary prevention with statins was complicated, depending on number of risk factors, low-density lipoprotein cholesterol (LDL-C) levels, and estimated 10-year risk (>20%: nearly unconditional treatment; 10-20%: conditional treatment).[6,7]

The 2010 revision of the NICE (National Institute for Health and Care Excellence) guideline recommended to estimate 10-year risk for CVD, defined by QRISK as CHD (angina and MI), stroke, and transient ischemic attack.[9,10] The latest version of the risk calculator, QRISK®2-2013, was used for this study.[11] When QRISK®2 is used outside UK, an average value for social deprivation (UK postcode) is used to calculate the score. For primary prevention in people aged 40-74, statin therapy was recommended at QRISK ≥20% (defined as high risk). The 2014 revision of the NICE guideline recommends to lower the risk-based threshold for primary prevention with statins from 20% to 10% in people ≤84 years of age,[12] endorsed by the third Joint British Societies’ (JBS3) consensus recommendations for the prevention of CVD.[13] Beyond age 84, the new recommendation 55 reads as follows; “For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation 48)”.[12]
Comparison of CVD prevention guidelines

We evaluated and compared the performance of the American and European primary prevention guidelines shown in Table 1 in the printed article. For each patient we calculated the absolute 10-year risk for the predicted outcomes using the recommended risk equations or calculators. In accordance with the SCORE risk charts [1] and the online risk calculator HeartScore,[2] the age-dependent risk was capped at age 65 when estimating risk using the SCORE algorithms. The guidelines were compared in three steps as described below.

First, we assessed the concordance in CVD risk characterization between the PCE and the four other risk equations/calculators (ATP III, QRISK2, SCORE+HDL low-risk and SCORE+HDL high-risk) by computing the Spearman rank-order correlation coefficients (Spearman's rho). Secondly, the new American ACC/AHA risk thresholds of 5% and 7.5% were translated to risks estimated by the other risk equations/calculators. The risk values estimated by ATP III, QRISK2 and SCORE+HDL that corresponded to PCE risks of 5% and 7.5% were determined from sex-specific linear regression equations derived from pairwise comparisons of predicted risk in persons with a PCE risk <7.5%. Finally, we determined the proportion of patients with a first MI who would have been eligible for primary prevention with statins based on recommendations in the former and the new American and European guidelines. Men and women were analyzed separately, and stratified by pre-specified age groups (40 to 60 years and 60 to 75 years).

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Available at: http://circ.ahajournals.org/content/106/25/3143.long


11. QRISK®2-2013 cardiovascular disease risk calculator. Available at: http://qrisk.org


**Supplementary Table**

Supplementary Table. Proportion of patients (detection rate) with first MI who had a predicted risk of atherosclerotic CVD above which primary prevention with statins should be considered.

<table>
<thead>
<tr>
<th>Guideline Algorithm</th>
<th>Risk threshold</th>
<th>Detection rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40-60 years of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men n=65</td>
</tr>
<tr>
<td>2012 ESC European Guideline SCORE+HDL Low-Risk¹</td>
<td>5%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>2012 ESC European Guideline SCORE+HDL High-Risk¹</td>
<td>5%</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>2013 ACC/AHA² Pooled Cohort Equations/White</td>
<td>5%</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>7.5%</td>
<td>62</td>
</tr>
<tr>
<td>Adult Treatment Panel III³ Modified Framingham Equation</td>
<td>10%</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>12</td>
</tr>
<tr>
<td>2010 &amp; 2014 NICE/UK⁴,⁵ QRISK2-2013/White</td>
<td>10%</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>2</td>
</tr>
</tbody>
</table>

¹Statin therapy should be considered at SCORE ≥5% below age 60 and ≥10% above 60.[1]
²Recommendations for statin therapy are 10-year risk ≥7.5% (strong/class I) and 5% to <7.5% (weak/class IIa).[2]
³Recommendations for statin therapy depending on risk factors, cholesterol level, and 10-year risk >20% (~unconditional treatment) and 10-20% (conditional treatment).[3]
⁴Indication for statin therapy in UK was 10-year risk ≥20% until 2014,[4] then lowered to ≥10% in the 2014 NICE guideline.[5]

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Supplementary Figure. Eligibility for statin therapy by high-risk versus low-risk SCORE equation.

Predicted risk estimated by the High-Risk and Low-Risk SCORE equations correlated perfectly (Spearman’s rho ≥0.99; R^2 = 0.99; p<0.0001). The High-Risk equation consistently overestimates risk compared with the Low-Risk equation. Classification based on the guideline-defined decision thresholds of 5% and 10% was discordant in 85 of 162 males (52%) and 27 of 85 females (32%), with potential loss of indication for statin therapy by recalibration of SCORE to fit a lower mortality of cardiovascular disease.

ESC: European Society of Cardiology.